What is claimed is:

1. A method for measuring *in vivo* blood glucose levels through the skin, said method comprising monitoring, in a population of cells one or more relevant metabolites, parameters or analytes in at least one metabolic pathway, wherein the monitoring comprises measuring the fluorescence spectrum emitted by a reporter composition located in the skin, wherein the fluorescence spectrum emitted by the reporter is stoichiometrically related to the metabolite, parameter or analyte concentration in the population of cells, whereby analyzing the relatedness provides the *in vivo* blood glucose level.

2. The method of claim 1, wherein the population of cells has a predominantly glycolytic metabolism or can be induced to have a glycolytic metabolism.

3. The method of claim 2, wherein the population of cells in the skin is located in the epidermis, wherein the epidermis comprises a dynamic, metabolically homogeneous, and homeostatic population of cells.

4. The method of claim 2, wherein the population of cells having a glycolytic metabolism comprise live keratinocytes.

5. The method of claim 4, wherein the live keratinocytes are present in the epidermal layer of skin.

6. The method of claim 5, wherein the live keratinocytes are present at a depth from the surface of the skin from about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer.

7. The method of claim 1, wherein the metabolic pathway is monitored within the population of cells via measurement of a specific metabolite or analyte of the glycolytic pathway that has a stoichiometric or highly correlated relationship with glucose concentration.

8. The method of claim 1, wherein the metabolic pathway is monitored within the population of cells, via a physico-chemical parameter that is related to the glycolytic pathway, wherein said parameter has a stoichiometric or highly correlated relationship with glucose concentration.

9. The method of claim 7, wherein the one or more relevant metabolites or analytes are selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; inorganic phosphate (P_i); glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide (phosphate), reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

10. A skin sensor composition, comprising one or more of:

a reporter dye and a marker dye; or

a dye exhibiting a wavelength shift in absorption or fluorescence emission in the presence of a metabolite;

wherein the skin composition is present at a depth from the surface of the skin from about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, in the epidermis at an effective concentration for detection of one or more metabolites or analytes in a metabolic pathway in a subject or biological sample.

11. The skin composition of claim 10, wherein the reporter dye is chosen from the group consisting of: a mitochondrial vital stain or dye, and a dye exhibiting one or more of a redox potential, an energy transfer properties, and a pH gradient.

12. The skin composition of claim 11, wherein the mitochondrial vital stain or dye is a polycyclic aromatic hydrocarbon dye selected from the group consisting of: rhodamine 123; di-4-ANEPPS; di-8-ANEPPS; $DiBAC_4(3)$; RH421; tetramethylrhodamine ethyl ester, perchlorate; tetramethylrhodamine methyl ester, perchlorate; 2-(4-(dimethylamino)styryl)-*N*-ethylpyridinium iodide; 3,3'-dihexyloxacarbocyanine, 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine chloride; 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine iodide; nonylacridine orange; dihydrorhodamine 123 dihydrorhodamine 123, dihydrochloride salt; xanthene; 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein; benzenedicarboxylic acid; 2(or 4)-[10-(dimethylamino)-3-oxo-3-H-benzo[c]xanthene-7-yl]; and iodine dissolved in potassium iodide.

13. The skin composition of claim 10, wherein the reporter dye is selected from the group consisting of: coumarin; derivatives of coumarin, anthraquinones; cyanine dyes, azo dyes; xanthene dyes; arylmethine dyes; pyrene derivatives; and ruthenium bipyridyl complexes.

14. The skin composition of claim 10, wherein the one or more metabolites or analytes is selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide phosphate, reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

15. The skin composition of claim 10, wherein the effective concentration is selected from the group consisting of at least between 1 to 500 μg/ml, between 5 to 150 μg/ml, and 10 to 100 μg/ml.

16. The skin composition of claim 15, wherein a specific application comprises a 5 μL volume of a 400 μM SMMR solution, or a 10 μL volume at 200 μM concentration.

17. The skin sensor composition of claim 10, wherein the one or more metabolites or analytes directly report on and relate to *in vivo* blood glucose levels.

18. The skin sensor composition of claim 17, wherein the related metabolites or analytes are selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide phosphate, reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

19. A method for monitoring the concentration of one or more metabolites or analytes, the method comprising:

applying the skin sensor composition according to claim 10 to a surface of the skin for a predetermined period of time;

causing penetration of the skin sensor composition to a depth of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, into the epidermis; and

monitoring a change in the concentration of the one or more metabolites or analytes in a metabolic pathway by detecting changes in one or more reporter dyes at one or more time points using an optical reader.

20. The method of claim 1, wherein the population of cells has a predominantly oxidative metabolism or can be induced to have a metabolism predominantly based on oxidative phosphorylation.

21. The method of claim 20, wherein the metabolic pathway is monitored within the population of cells via a metabolite or analyte that is generated as a result of the oxidative metabolic pathway and that has a stoichiometric or highly correlated relationship with glucose concentration.

22. The method of claim 20, wherein the metabolic pathway is monitored within the population of cells via a physico-chemical parameter that is generated as a result of the oxidative metabolic pathway and that has a stoichiometric or highly correlated relationship with glucose concentration.

23. The method of claim 19, wherein the skin sensor composition comprises a mitochondrial stain sensitive to membrane potential or chemical gradient.

24. The method of claim 19, wherein the skin sensor composition comprises a dye or stain that transfers energy from a molecule generated as a result of the oxidative metabolic pathway and that has a stoichiometric or highly correlated relationship with glucose concentration.

25. The method of claim 23, wherein the mitochondrial stain is a polycyclic aromatic hydrocarbon dye selected from the group consisting of: rhodamine 123; di-4-ANEPPS; di-8-ANEPPS; $DiBAC_4(3)$; RH421; tetramethylrhodamine ethyl ester, perchlorate; tetramethylrhodamine methyl ester, perchlorate; 2-(4-(dimethylamino)styryl)-*N*-ethylpyridinium iodide; 3,3'-dihexyloxacarbocyanine, 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine chloride; 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine iodide; nonylacridine orange; dihydrorhodamine 123 dihydrorhodamine 123, dihydrochloride salt; xanthene; 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein; benzenedicarboxylic acid; 2(or 4)-[10-(dimethylamino)-3-oxo-3-H-benzo[c]xanthene-7-yl]; and iodine dissolved in potassium iodide.

26. The method of claim 19, wherein the skin sensor composition comprises a dye selected from the group consisting of: coumarin; derivatives of coumarin; anthraquinones; cyanine dyes; azo dyes; xanthene dyes; arylmethine dyes; pyrene derivatives; and ruthenium bipyridyl complexes.

27. The method of claim 19, wherein the one or more metabolites or analytes is selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; inorganic phosphate (P_i); glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide phosphate, reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); and flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

28. The method of claim 19, wherein the skin sensor composition is formulated as any one or more of the following: an emulsion, an ointment, a disposable gel film patch, a reservoir device, a cream, a paint, polar solvents or non-polar solvents.

29. The method of claim 19, wherein the penetration of the skin composition is accomplished using an active transport technique or a passive transport technique selected from the group consisting of: electroporation, laser poration, sonic poration, ultrasonic poration, iontophoresis, mechanical-poration, solvent transport, tattooing, wicking, and pressurized delivery.

30. The method of claim 19, wherein the penetration of the skin sensor composition to a depth of about 10 μm to about 175 μm is accomplished by combining the composition with molecular size attachments.

31. The method of claim 19, where the predetermined period of time is selected from the group consisting of at least 24-48 hours, at least 2-6 hours, from about 5 seconds to 5 minutes, and from about 30 seconds to 5 minutes.

32. The method of claim 19, where monitoring the change in metabolite or analyte concentration comprises detecting at least one wavelength above 450 nm.

33. A method for monitoring *in vivo* blood glucose levels, the method comprising:

applying the skin sensor composition according to claim 10 to a surface of the skin for a predetermined period of time;

causing penetration of the skin sensor composition to a depth of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, into the epidermis;

monitoring a change in the concentration of the one or more metabolites or analytes by detecting changes in the reporter dye using an optical reader, and

correlating the change in the concentration of the one or more metabolites or analytes with *in vivo* blood glucose levels.

34. The method of claim 33, wherein the skin sensor composition comprises a mitochondrial vital stain or dye, or a dye exhibiting redox potential or energy transfer properties.

35. The method of claim 34, wherein the mitochondrial vital stain or dye is at least one polycyclic aromatic hydrocarbon dye selected from the group consisting of: Rhodamine 123, Di-4-ANEPPS; Di-8-ANEPPS, $DiBAC_4(3)$, RH421, Tetramethylrhodamine ethyl ester, perchlorate, Tetramethylrhodamine methyl ester, perchlorate, 2-(4-(dimethylamino)styryl)-*N*-ethylpyridinium iodide, 3,3'-Dihexyloxacarbocyanine, 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine chloride, 5,5',6,6'-tetrachloro-1,1',3,3' -tetraethyl-benzimidazolylcarbocyanine iodide, Nonylacridine Orange, Dihydrorhodamine 123 and Dihydrorhodamine 123, dihydrochloride salt; xanthene; 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein; benzenedicarboxylic acid; 2(or 4)-[10-(dimethylamino)-3-oxo-3-H-benzo[c]xanthene-7-yl]; and iodine dissolved in potassium iodide.

36. The method of claim 33, wherein the skin sensor composition comprises at least one dye selected from the group consisting of: coumarin, derivatives of coumarin, anthraquinones, cyanine dyes, azo dyes, xanthene dyes, arylmethine dyes, pyrene derivatives, and ruthenium bipyridyl complexes.

37. The method of claim 33, wherein the one or more metabolites or analytes is selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide phosphate, reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

38. The method of claim 33, wherein the skin sensor composition is formulated as an emulsion, cream, ointment, disposable gel film patch, reservoir device, paint, or solvent mixture.

39. The method of claim 33, wherein the penetration of the skin composition is accomplished using at least one active transport or passive transport technique selected from the group consisting of: electroporation, laser poration, sonic poration, ultrasonic poration, solvent transport, iontophoresis, mechanical-poration, tattooing, painting, wicking and pressurized delivery.

40. The method of claim 33, wherein the penetration of the skin sensor composition to a depth of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, is accomplished by combining the composition with molecular size attachments.

41. The method of claim 33, where the predetermined period of time is selected from the group consisting of at least 24-48 hours, at least 2-6 hours, from about 5 seconds to 5 minutes, and from about 30 seconds to 5 minutes.

42. The method of claim 33, where monitoring the change in the one or more metabolite or analyte concentrations comprises measuring at least one spectral emission at a wavelength above 450 nm.

43. The method of claim 33, wherein the one or more metabolites are selected from the group consisting of: lactate; hydrogen ion (H^+); calcium ion (Ca^{2+}) pumping rate; magnesium ion (Mg^{2+}) pumping rate; sodium ion (Na^+) pumping rate; potassium ion (K^+) pumping rate; adenosine triphosphate (ATP); adenosine diphosphate (ADP); the ratio of ATP to ADP; glycogen; pyruvate; nicotinamide adenine dinucleotide phosphate, oxidized form (NAD(P)+); nicotinamide adenine dinucleotide phosphate, reduced form (NAD(P)H); flavin adenine dinucleotide, oxidized form (FAD); flavin adenine dinucleotide, reduced form ($FADH_2$); and oxygen (O_2) utilization.

44. A sensor system, the system comprising:

a device comprising a component that transmits radiation to a material or tissue, a component that detects radiation emitted from a material or tissue, and a component to display the detection results;

an applicator that delivers the skin sensor composition of claim 10 to the material or tissue; and

an air interface between the device and the material or tissue, wherein the air interface measures a resulting excitation radiation emitted from the irradiated skin sensor composition.

45. The sensor system of claim 44, wherein said system comprises a device that emits radiation at one or more wavelengths chosen to specifically excite the skin composition that is applied to the material or tissue, wherein the skin sensor composition comprises one or more of:

a reporter dye and a marker dye; or

a dye exhibiting a wavelength shift in absorption or fluorescence emission in the presence of a metabolite;

wherein the skin sensor composition is present at a depth from the surface of the skin of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer, in the epidermis at an effective concentration for detection of one or more metabolites or analytes in a biological sample.

46. The sensor system of claim 44, wherein said system detects radiation at one or more wavelengths chosen to specifically identify fluorescence emission scattered back to the system from the skin sensor composition.

47. A method for determining blood glucose concentration, comprising the steps of:

performing an instrument response measurement on a calibration target and recording the response data;

applying a dye mixture to the skin in a first small controlled spot such that the dye resides in the epidermal layer of the skin;

applying a second dye mixture to the skin in a second small controlled spot and perturbing the second spot such that one or more extreme changes that the mixture may undergo are achieved;

performing a calibration measurement on the perturbed spot and recording the calibration data;

performing a background measurement on an area of skin that has no dye and recording this background data;

performing a measurement on the first spot by illuminating the first spot with light;

detecting wavelength spectrum of light reflected back from the first spot;

performing further measurements on the first spot at wavelengths suitable for each dye present;

calculating a parameter from the response data to normalize the background, calibration and measurement data for the response of the spectrometer;

calculating a parameter from the background data to correct the calibration and measurement data for emission, absorption and scattering properties of the tissue;

calculating a metabolite parameter from the calibration data to relate the measurement data to the blood glucose concentration.

48. The method of claim 47, wherein the one or more extreme changes is a change in concentration of the metabolite or analyte between a zero or low concentration and a saturation level or high concentration.

49. A method of calculating a blood glucose concentration, said method comprising:

measuring a background response and an autofluorescence tissue response from a calibration target comprising an epidermal layer of skin;

providing a first dye to a first skin location and causing residues of the first dye mixture to transfer into the epidermal layer of the skin;

providing a second dye to a second skin location and causing and recording at least one extreme change in the mixture;

illuminating the first skin location with a radiative emission;

detecting a resulting wavelength spectrum reflected from the first skin location;

optionally repeating the illuminating and detecting steps using irradiation and wavelength spectra associated with each dye provided; and

detecting at least one physico-chemical parameter that is related to the glycolytic pathway, wherein said parameter comprises a stoichiometric or highly correlated relationship with glucose concentration;

thereby determining the blood glucose concentration.

50. The method of claim 49, wherein the sensor system comprises a bloodless calibration procedure as outlined in one or more of equations 13, 16, 17, 18, 19, 20 or 21.

51. The method of claim 49, wherein the at least one extreme change is a change in the blood glucose concentration between a zero or low concentration and a saturation level or high concentration.

52. A method for determining the concentration of at least one metabolite or analyte in skin tissue, the method comprising:

(a) administering to the skin tissue a small molecule metabolite reporter (SMMR) agent;

(b) causing penetration of the SMMR agent to a region of the skin at a depth between the dermis and the epidermis, wherein the depth from the surface of the skin is from about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about 175 μm, wherein said depth corresponds with the top of the dermal layer;

(c) irradiating the SMMR agent in the skin tissue with a source of electromagnetic radiation;

(d) measuring the fluorescence spectra emitted from the SMMR agent; and

(e) analyzing the emitted fluorescence spectra;

wherein the analysis will result in a determination of the concentration of the metabolite or analyte.

53. The method of claim 50, wherein the measuring of the fluorescence spectra comprises a bloodless calibration procedure as outlined in one or more of equations 13, 16, 17, 18, 19, 20 and 21.